This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 2150.

See reverse side for additional information.

Interagency Report Control No
0180-DOA-AN

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

ANNUAL REPORT OF RESEARCH FACILITY

(TYPE OR PRINT)

1. REGISTRATION NO. 14-R-0162

CUSTOMER NO. 17008

FORM APPROVED
OMB NO. 0579-0036

Kb

2. HEADQUARTERS RESEARCH FACILITY *(Name and Address, as registered with USDA, include Zip Code)*

NUCRYST PHARMACEUTICALS
50 AUDUBON RD
SUITE B
WAKEFIELD, MA 01880
~~(781) [illegible]~~ 781-224-1444

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, teaching, or experimentation, or held for these purposes. Attach additional sheets if necessary.)

FACILITY LOCATIONS*(sites)*

See Attached Listing

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY *(Attach additional sheets if necessary or use APHIS FORM 7023A)*

A. Animals Covered By The Animal Welfare Regulations	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic,analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. *(An explanation of the procedures producing pain or distress in these animals and the reasons such drugs were not used must be attached to this report)*	F. TOTAL NO. OF ANIMALS (Cols. C + D + E)
4. Dogs					
5. Cats					
6. Guinea Pigs					
7. Hamsters	0	58	392	241	691
8. Rabbits					
9. Non-Human Primates					
10. Sheep					
11. Pigs					
12. Other Farm Animals					
13. Other Animals					

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). **A summary of all the exceptions is attached to this annual report.** In addition to identifying the IACUC-approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional official)

I certify that the above is true, correct, and complete (7 U.S.C. Section 2143)

(b)(6), (b)(7)c

DATE SIGNED 28-Nov-07

1 - HEADQUARTERS

(AUG 91)

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Column E Explanation

This form is intended as an aid to completing the Column E explanation. It is not an official form and its use is voluntary. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A Column E explanation must be written so as to be understood by lay persons as well as scientists.

1. Registration Number: 14-R-0162
2. Number 691 of animals used in this study.
3. Species (common name) Hamster of animals used in the study.
4. Explain the procedure producing pain and/or distress.

   Please see attached letter

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below)

6. What, if any, federal regulations require this procedure? Cite the agency, the code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

   Agency__________ CFR__________

NUCRYST™
PHARMACEUTICALS

(b)(6), (b)(7)c
Associate Director, Microbiology and Immunology

28 November 2007

Elizabeth Goldentyer, DVM
Regional Director, Animal Care
USDA-APHIS Eastern Regional Office
920 Main Campus Drive, Suite 200, Unit 3040
Raleigh, NC 27606

Subject: Annual Report of Research Facility for 1 Oct 2006 through 30 Sept 2007
USDA Registration # 14-R-0162

Dear Dr. Goldentyer:

Attached please find our Annual Report (form 7023) pertaining to research activities at Nucryst Pharmaceuticals, Inc. The use of covered animal species reported in USDA Category E (animal pain and/or distress without alleviation) is explained below.

> Syrian Hamsters were used to test the antibacterial activity of nanocrystalline silver in a model of *Clostridium difficile* post-antibiotic colitis [also called C difficile associated disease (CDAD), antibiotic associated diarrhea (AAD), or C difficile cecitis]. Disease is induced when the hamster is given a single oral dose of the antibiotic clindamycin, which is presumed to decimate the normal healthy bacterial flora in the GI tract, creating an environmental niche for C difficile to expand and overproduce cytotoxins. After induction with clindamycin, animals are assigned to treatment groups receiving nanocrystalline silver or control treatments. Negative controls include untreated animals and animals receiving only the vehicle used to deliver the nanocrystalline silver. Vancomycin was used as the positive control since it is approved by the FDA for the treatment of CDAD in humans, and has a consistently high success rate in hamsters. Animals received 1 to 3 treatments per day, and were monitored for signs of disease including: stool cultures that were positive for C difficile, diarrhea, weight loss, tachypnea, piloerection, and changes in grooming behavior. All of these characteristics except stool culture were monitored at least twice per day. Animals that appeared moribund were immediately euthanized by CO_2 asphyxiation; such animals were considered to have had lethal disease for the purposes of endpoint data.
>
> In the experiments performed at Nucryst to date, nearly 100% of hamsters induced with clindamycin acquired C difficile, and the rate at which disease progressed to death was dependent on the strain of C difficile used, consistent with the published literature. For the purposes of Categorization, only control animals that were not induced with clindamycin were placed in Category C. The number of uninduced control animals was kept to a minimum, and this condition was used only to train on experimental techniques at the start of the protocol or to validate the clindamycin-dependence of the disease model. Category D was assigned to animals that either received effective therapy (those that received antibacterial treatment and survived) or to those that were euthanized. The small proportion of animals that were induced with clindamycin, were not treated, but showed no outward signs of disease were placed in Category D rather than Category C. This was a conservative decision based on the near-100% acquisition of C difficile bacteria, and the natural tendency of

hamsters to maintain normal behavior even when under distress. Category E was assigned to animals that were discovered dead, and were usually those that died in the middle of the night.

The Syrian hamster is one of four established small animal models of C difficile associated disease, the three others being mouse, rat, and guinea pig. The mouse and rat models demonstrate low-to-no lethality, which has been experimentally linked to an insensitivity of these rodent species to the protein toxins produced by C difficile (Lyerly, et al 1985 Infect Immun 47:349-52). This feature, unfortunately, makes the mouse and rat models poor correlates of human disease, since the latter is strongly dependent on the action of these C difficile toxins. Hamsters and guinea pigs are susceptible to the C difficile toxins. This makes these two animal models excellent correlates of human disease, but has the drawback that these models are ultimately lethal and euthanasia frequently must be provided. The hamster model was chosen over the guinea pig model since the hamster is the lower species. In addition to the susceptibility of hamsters to C difficile toxins, the hamster model also responds to antibiotic treatments in a manner that is highly predictive of human patient responses. Therefore, despite the inherent lethality, the Syrian hamster model is the preferred model for CDAD therapeutics research.

The use of analgesics during this procedure was given careful consideration, but was decided against due to concern of the undesired, unintended effects such analgesics may have on the development and the treatment of the disease state being studied. Specifically, since CDAD is a gastrointestinal infectious disease inextricably linked to the host animal's immune status and nutritional status, the investigators are concerned over the reported loss of appetite among human volunteers after opioid use (Yeomans and Gray 1997 Physiol Behav 62:15-21), and nausea associated with the use of buprenorphine (Fullerton, et al 1991 Pharmacotherapy 11:90-93). Other related areas of concern are published studies demonstrating immunosuppressive (Volker, et al 2000 Lab Anim 34:423-429) or unpredictable immunomodulatory effects (Van Loveren, et al 1994 Lab Anim 28:355-363) of buprenorphine. Because of these factors, the Principal Investigator reluctantly decided to forego the provision of analgesics.

Please contact me at 781-246-6033 if you require any additional explanation regarding our USDA Annual Report.

Sincerely,

(b)(6), (b)(7)c

NUCRYST Pharmaceuticals, Inc.